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ORIGINAL ARTICLE

Neuroendocrine Liver Metastasis: Prognostic Implications of Primary Tumor Site on Patients Undergoing Curative Intent Liver Surgery

Gaya Spolverato, MD[1] · Fabio Bagante, MD[1] · Luca Aldrighetti, MD[2] · George Poultsides, MD[3] · Todd W. Bauer, MD[4] · Ryan C. Field, MD[5] · Hugo P. Marques, MD[6] · Matthew Weiss, MD[7] · Shishir K. Maithel, MD[8] · Timothy M. Pawlik, MD, MPH, PhD[9]

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Abstract

Background Neuroendocrine tumors typically arise from pancreatic (PNET) vs. gastrointestinal or thoracic origins (non-PNET). The impact of primary tumor site on long-term prognosis following resection of neuroendocrine liver metastasis (NELM) remains poorly defined. The objective of the current study was to define the association of primary tumor location on prognosis of patients undergoing curative intent liver resection for NELM.

Methods Between 1990 and 2014, 421 patients who underwent resection of NELM were identified from a multi-institutional database. Clinicopathological characteristics, operative details, and outcomes were stratified and analyzed by location of the primary tumor (PNET vs. non-PNET). A propensity score-matched analysis was utilized to assess the impact of primary tumor location on long-term survival.

Results Among the 421 patients, 197 (46.8%) patients had NELM from a PNET primary while 224 (53.2%) had a non-PNET primary (small bowel, $n = 145$; rectal, $n = 10$; bronchial, $n = 22$; other, $n = 47$). There were no differences in tumor burden and tumor site, while presence of extrahepatic disease was more common among patients with non-PNET NELM (extrahepatic disease, PNET NELM, $n = 11$ 27.5% vs. non-PNET NELM, $n = 29$ 72.5%; $p = 0.010$). Patients with PNET NELM were more likely to have non-functional disease compared with patients who had non-PNET NELM (non-functional, PNET NELM, $n = 117$ 54.9% vs. non-PNET NELM, $n = 96$ 45.1%; $p = 0.011$). On the final pathological specimen of the resected NELM, patients with PNET NELM were more likely to have a moderately differentiated tumor (59.3%), while patients with non-PNET NELM were more likely to have a poorly differentiated tumor (67.8%) ($p = 0.005$). Patients with PNET NELM had a worse 5-year DFS and 5-year OS compared with patients who had non-PNET NELM (DFS, PNET 36.2% vs. non-PNET 55.2%; $p = 0.001$ and OS, PNET 79.5% vs. non-PNET 83.4%; $p = 0.008$). After propensity score matching, both 5-year DFS and 5-year OS of the PNET and non-

Gaya Spolverato and Fabio Bagante equally contributed to the manuscript.

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✉ Timothy M. Pawlik, MD, MPH, PhD
tim.pawlik@osumc.edu

[1] Department of Surgery, University of Verona, Verona, Italy

[2] Scientific Institute San Raffaele, Milan, Italy

[3] Stanford University, Stanford, CA, USA

[4] University of Virginia, Charlottesville, VA, USA

[5] School of Medicine, Washington University, St Louis, MO, USA

[6] Curry Cabral Hospital, Lisbon, Portugal

[7] Johns Hopkins Hospital, Baltimore, MD, USA

[8] Emory University, Atlanta, GA, USA

[9] Department of Surgery, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

PNET groups were comparable (DFS, PNET 46.2% vs. non-PNET 55.9%; $p = 0.22$ and OS, PNET 81.5% vs. non-PNET 84.3%; $p = 0.19$).

Conclusion PNET patients more often present with non-functional NELM and moderately differentiated tumors. On propensity-matched analysis, factors such as extrahepatic disease and tumor grade, but not primary tumor location, were associated with prognosis of patients undergoing curative intent liver surgery for NELM.

Keywords NELM · Surgery · PNET · Pancreatic neuroendocrine tumor · Neuroendocrine liver metastasis

Introduction

Neuroendocrine tumors (NET) are a heterogeneous group of rare and typically slow-growing tumors with varied histologic features that arise most commonly from the pancreas and the luminal gastrointestinal tract.[1] NET are often hormone-secreting tumors, causing a wide range of hormonal syndromes, sometimes characterized by severe symptoms that can negatively impact quality of life.[2] Specifically, in a subset of patients with functional tumors, NET can cause debilitating hormonal symptoms, such as flushing, palpitations, as well as diarrhea.[3–8] Thus, treatment goals for NET should include both prolongation of survival, as well as NET-related symptom alleviation.[2]

Although the natural history of NET is often indolent and can be characterized by slow progression,[9] up to 60–80% of patients can present with synchronous or develop metachronous neuroendocrine liver metastasis (NELM) during the course of their disease. The presence of metastatic disease, perhaps not surprisingly, has been reported to be one of the strongest predictors of survival.[10–12] Indeed, the 5-year overall survival (OS) of patients with NELM ranges from 13 to 54 vs. 75–99% for patients with NET who do not have NELM.[12–14] Since many patients with NELM die of progressive liver disease,[1] the utilization of liver directed therapies, including hepatic resection, remains central to the treatment of patients with NELM.[15–17] Following liver resection, while 5-year survival can be as high as 60–75%, recurrence is much more common with up to 75–90% of patients experiencing a recurrence within 5 years.[15] In fact, our group had previously reported that the probability of being "cured" from NELM by liver surgery was only 44%.[18]

Multiple clinicopathological factors have been proposed as having an impact on the long-term prognosis of patients following resection of NELM. In particular, we recently reported a non-mixture cure fraction statistical model to estimate survival following resection.[18] The model identified type of NET, grade of tumor differentiation, and extent of liver involvement as being independent predictors of cure. In a separate study of the Italian Neuroendocrine Liver Metastasis Database, Ruzzenente et al. identified number of NELM, tumor size, and Ki-67 index as prognostic factors associated with the prognosis of patients undergoing liver resection of NELM.[4] Moreover, Mayo et al. reported that hormonal status and presence of extrahepatic disease were associated with long-term survival, while R0 resection was associated with improved outcomes only among patients with functional tumors.[19] Despite these previous studies, the impact of primary tumor site on long-term prognosis following resection of NELM remains poorly defined. As such, the objective of the current study was to assess the impact of pancreatic (PNET) vs. gastrointestinal or thoracic (non-PNET) primary tumor site on the prognosis of patients undergoing curative intent hepatic resection of NELM.

Materials and Methods

Patient Demographic and Clinical Data

Patients were identified from a neuroendocrine liver metastases database that included 421 patients who underwent multimodal treatments for NELM from 1990 to 2014 at one of seven major hepatobiliary institutions (Johns Hopkins Hospital, Baltimore, MD; Stanford University, Stanford, CA; Washington University School of Medicine, St Louis, MO; University of Virginia, Charlottesville, Virginia; Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; Curry Cabral Hospital, Lisbon, Portugal; Winship Cancer Institute, Emory University, Atlanta, GA). Only patients who had either simultaneous or staged surgical resection of both the primary tumor and the liver metastases were included in the study cohort. Patients who received only non-surgical treatments (e.g., embolization, ablation, etc.) and/or did not undergo surgical resection of the primary NET were excluded from the analyses. The Institutional Review Board of all the participating institutions approved the study.

Standard demographic and clinicopathologic data were collected including age, gender, disease functional status, liver tumor burden, liver tumor site, and primary tumor lymph node status, margin status, grade of differentiation, and presence of extrahepatic disease. According to the 2010 WHO grading system, tumor grade was classified as well (G0), moderately (G1), or poorly (G3) differentiated; if histologic grade varied in a specific specimen, the "worst" grade was used as the index tumor grade.[20] A R0 resection was defined as the absence of macroscopic or microscopic disease

at the surgical margin, while a R1 resection was classified as microscopic presence of tumor and R2 was classified as macroscopic presence of tumor (debulking). Nodal status was ascertained based on final pathologic assessment. Treatment-related variables were also included, such as type of treatment before surgery, type of liver surgery, receipt of intraoperative ablation, and receipt of adjuvant treatment. Data on type of surgery were collected with major hepatic resection defined as resection of at least three full Couinaud segments.[21] Hepatic resection was performed with a variety of techniques.[22] NELM primary NET sites included pancreas (PNET), gastrointestinal tract (G-NET), and tracheo-bronchopulmonary complex (TB-NET) neuroendocrine tumors. For the purposes of analyses, primary tumor site was categorized as pancreatic (PNET) vs. gastrointestinal or thoracic (non-PNET).

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQR) while categorical variables were reported as whole numbers and percentages. The primary outcome of interest was OS; the secondary outcome was disease-free survival (DFS). OS was defined as the time interval between the date of surgery and the date of death. Time was censored at the date of last follow-up for living patients. DFS was defined as the time interval between the date of surgery and the date of recurrence. Time was censored at the date of last follow-up for patients who were noted to be free of disease. Date of last follow-up and vital status were collected for all patients. Clinicopathological characteristics, operative details, and outcomes were stratified and analyzed by location of the primary tumor ((PNET) vs. (non-PNET)).

To account for any potential residual confounding when assessing the effect of NET primary site on survival, propensity scores were estimated using a logistic regression model with binary outcomes specified as PNET vs. non-PNET. Gender, grade of tumor differentiation, lymph node status, functional status, synchronous disease, preoperative treatment, liver involvement, extrahepatic disease, margin status, and adjuvant treatment were included as independent variables in the logistic regression model. A caliper width of 0.1 times the standard deviation of the propensity score was used for matching; one-to-one matching without replacement was used to identify 132 PNET and 132 non-PNET matched patients. The degree of covariate imbalance in unmatched and matched samples was measured using the standardized (mean and proportion) differences. All analyses were carried out with STATA version 12.0 (StataCorp, College Station, TX). All tests were two-sided and a p value <0.05 was considered statistically significant.

Results

Demographic and Clinicopathologic Characteristics

A total of 421 patients who underwent hepatic resection for NELM met the inclusion criteria and were included in the study cohort (Table 1). Median patient age was 58 years (interquartile range, 49.0–67.9) and half of patients were female (n = 219, 52.0%). The tumor was well, moderately, and poorly differentiated in 173 (54.4%), 86 (27.0%), and 59 (18.6%), respectively. Lymph node metastasis occurred in 213 (56.5%) patients. Liver metastases were synchronous in 259 (61.8%) patients and metachronous in 160 (38.2%) patients. The majority of patients (n = 285, 76.0%) did not receive any additional treatment before hepatectomy, while 63 (16.8%) and 27 (7.2%) patients had received octreotide or chemotherapy, respectively. NELM involved >75%, 75–50%, 50–25%, and >25% of the liver in 190 (49.2%), 120 (31.1%), 62 (16.1%), and 14 (3.6%) patients, respectively. NELM disease was bilateral in 217 (57.3%) patients; extrahepatic disease was diagnosed in 40 (9.5%) patients. At the time of surgery, intraoperative tumor ablations were performed in 90 (21.5%) patients. Final surgical margin status was R0, R1, and R2 in 279 (68.9%), 95 (23.5%), and 31 (7.6%), respectively. The majority of patients (n = 177, 56.9%) did not receive any adjuvant treatment, while 97 (31.2%) and 37 (11.9%) patients received post-operative octreotide and chemotherapy, respectively.

The primary NET was pancreatic in 197 (46.8%) patients vs. gastrointestinal tract or other organs (i.e., tracheobronchopulmonary, lung, etc.) in 224 (53.2%) patients. As expected, there were differences in the baseline clinicopathological characteristics of patients with NELM from PNET vs. non-PNET primary tumors. While there were no differences in age and gender, patients with PNET-derived NELM were more likely to have non-functional disease compared with patients who had non-PNET-derived NELM (non-functional, PNET NELM, n = 117 54.9% vs. non-PNET derived NELM, n = 96 45.1%; p = 0.011). There were no differences in tumor burden and tumor site, while presence of extrahepatic disease was more common among patients with non-PNET-derived NELM (extrahepatic disease, PNET-derived NELM, n = 11 27.5% vs. non-PNET derived NELM, n = 29 72.5%; p = 0.010). Presence of synchronous primary tumor and NELM was comparable among patients with a primary pancreatic NET and other primary NET. There was also no difference in terms of type of surgery; 94 (43.7%) patients with PNET-derived NELM underwent a major liver resection compared with 121 (56.3%) patients with non-PNET-derived NELM (p = 0.20). Intraoperative tumor ablation was common among both groups (PNET-derived NELM 48.9% vs. non-PNET-derived NELM 51.1%). On the final pathological NELM specimen, patients with PNET-

derived NELM were more likely to have a moderately differentiated tumor (59.3%), while patients with non-PNET-derived NELM were more likely to have a poorly differentiated tumor (67.8%) (p = 0.005). Patients with PNET-derived NELM were slightly less likely to have lymph node metastasis (43.7%) compared with patients who had non-PNET-derived NELM (56.3%) (p = 0.09). Margin status was comparable between the two groups (p = 0.96). Among patients who received any type of adjuvant treatment, octreotide was more commonly administered to patients with non-PNET-derived NELM, while chemotherapy was more common among patients with PNET-derived NELM (p < 0.001).

Table 1 Clinical and pathologic features of patients (n = 421)

Variables	Entire cohort *N* (%)	Pancreas *N* (%)	Non-pancreas *N* (%)	*p* value
Patients		197	224	–
Age, median (IQR)	58 years (49.0–67.9)	58 years (48–69)	59 years (50–67)	0.96
Gender				0.38
Female	219 (52.0)	107 (48.9)	112 (51.1)	
Male	202 (48.0)	90 (44.6)	112 (55.4)	
Functional status				0.011
Non-functional	213 (63.8)	117 (54.9)	96 (45.1)	
Functional	121 (36.2)	49 (40.5)	72 (59.5)	
NA/missing	87	31	56	
Grade of differentiation				0.005
Well	173 (54.4)	77 (44.5)	96 (55.5)	
Moderate	86 (27.0)	51 (59.3)	35 (40.7)	
Poor	59 (18.6)	19 (32.2)	40 (67.8)	
NA/missing	103	50	53	
Primary tumor lymph node status				0.09
N0	164 (43.5)	86 (52.4)	78 (47.6)	
N1	213 (56.5)	93 (43.7)	120 (56.3)	
NA/missing	44	18	26	
Synchronous disease				0.71
No	160 (38.2)	73 (45.6)	87 (54.4)	
Yes	259 (61.8)	123 (47.5)	136 (52.5)	
NA/missing	2	1	1	
Treatment before liver surgery				0.005
None	285 (76.0)	127 (44.6)	158 (55.4)	
Octreotide	63 (16.8)	25 (39.7)	38 (60.3)	
Chemotherapy	27 (7.2)	21 (77.7)	6 (22.3)	
NA/missing	46	24	22	
Liver involvement				0.19
>25%	14 (3.6)	5 (35.7)	9 (64.3)	
25–50%	62 (16.1)	28 (45.2)	34 (54.8)	
50–75%	120 (31.1)	45 (37.5)	75 (62.5)	
<75%	190 (49.2)	94 (49.5)	96 (50.5)	
NA/missing	35	25	10	
Location				0.21
Unilobar	162 (42.7)	83 (51.2)	79 (48.8)	
Bilobar	217 (57.3)	97 (44.7)	120 (55.3)	
NA/missing	42	17	25	
Intraoperative tumor ablation				0.67
No	328 (78.5)	152 (46.3)	176 (53.7)	
Yes	90 (21.5)	44 (48.9)	46 (51.1)	
NA/missing	3	1	2	
Extrahepatic disease				0.01
No	381 (90.5)	186 (48.8)	195 (51.2)	
Yes	40 (9.5)	11 (27.5)	29 (72.5)	
Margin status				0.96
R0	279 (68.9)	128 (45.9)	151 (54.1)	
R1	95 (23.5)	43 (45.3)	52 (54.7)	
R2	31 (7.6)	15 (48.4)	16 (51.6	
NA/missing	16	11	5	
Adjuvant therapy				<0.001
None	177 (56.9)	100 (56.5)	77 (43.5)	
Octreotide	97 (31.2)	30 (30.9)	67 (69.1)	
Chemotherapy	37 (11.9)	30 (81.1)	7 (18.9)	
NA/missing	110	37	73	
Disease-free survival, 5 years (95% CI)	46.2% (40.3–51.9)	36.2% (28.2–44.3)	55.2% (46.8–62.8)	0.001
Overall survival, 5 years (95% CI)	81.5% (76.7–85.4)	79.5% (72.2–85.1)	83.4% (76.6–88.4)	0.008

NA/missing not available/missing

Long-Term Outcomes of Patients with NELM from PNET and Non-PNET

Within a median follow-up of 4.6 years, the 1-, 3-, and 5-year DFS was 80.2, 57.5, and 46.2%, respectively; the 3-, 5-, and 10-year OS was 89.4, 81.5, and 65.2%, respectively. Patients with PNET-derived NELM had a worse 5-year DFS and 5-year OS compared with patients who had non-PNET-derived NELM (DFS, PNET 36.2% vs. non-PNET 55.2%; $p = 0.001$ and OS, PNET 79.5% vs. non-PNET 83.4%; $p = 0.008$) (Fig. 1).

A number of factors including location of the primary NET, functional status, grade of tumor differentiation, lymph node status, timing of primary and metastatic tumor, presence of extrahepatic disease, and liver tumor burden were each associated with 10-year OS (Table 2). Particularly, patients with PNET-derived NELM had a markedly worse 10-year OS of 58.2% (95% CI, 48.2–66.9) vs. 71.6% (95% CI, 62.6–78.8) for patients with non-PNET-derived NELM ($p = 0.008$). Moreover, patients with a non-functional PNET-derived NELM had a much worse OS of 54.8% (95% CI, 43.7–64.5) compared with 75.0% (95% CI, 63.3–83.4) for non-PNET-derived NELM ($p < 0.001$). Patients with well, moderate, and poor tumor grade differentiation had a 10-year OS of 80.4% (95% CI, 71.1–87.1), 58.2% (95% CI, 40.5–72.3), and 51.9% (95% CI, 33.2–67.8), respectively ($p = 0.001$). Similarly, tumor burden and site were associated with prognosis. Specifically, 10-year OS was 58.4% (95% CI, 46.5–68.6) for patients with >75% liver involvement, 66.6% (95% CI, 53.8–76.6) for patients with 75–50% liver involvement, 71.0% (95% CI, 56.4–81.5) for patients with 50–25% liver involvement, and 92.3% (95% CI, 56.6–99.9) for patients with <25% liver involvement ($p < 0.027$). Similarly, patients with extrahepatic disease had a worse OS of 42.8% (95% CI, 23.2–61.2) compared with 67.8% (60.8–78.7) for patients without extrahepatic disease. On the final pathological specimen, presence of lymph node metastasis and R1-R2 resections were associated with worse outcome (Table 2).

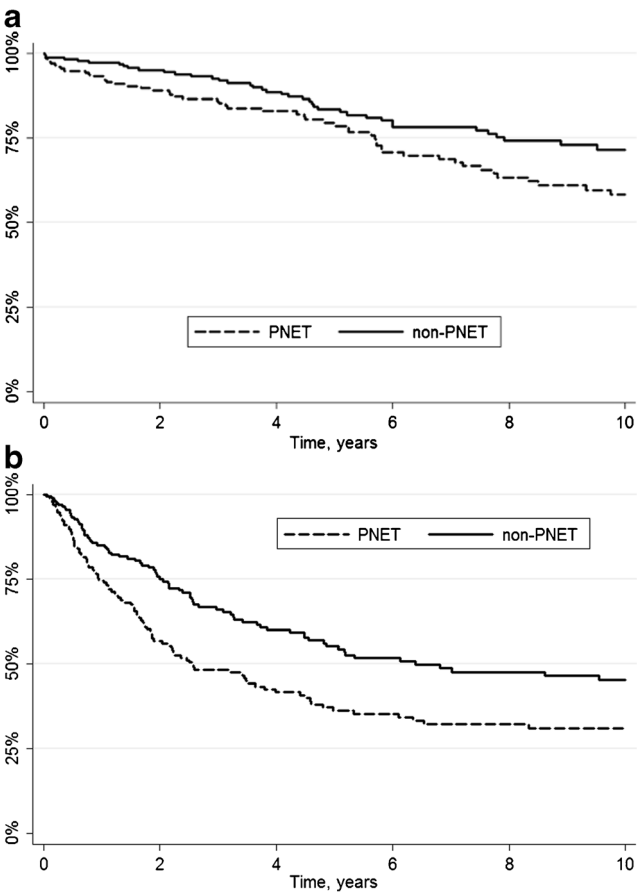

Fig. 1 **a** Kaplan-Meier OS survival curve comparing PNET vs. non-PNET-derived NELM NET. **b** Kaplan-Meier survival DFS curve comparing PNET vs. non-PNET-derived NELM NET

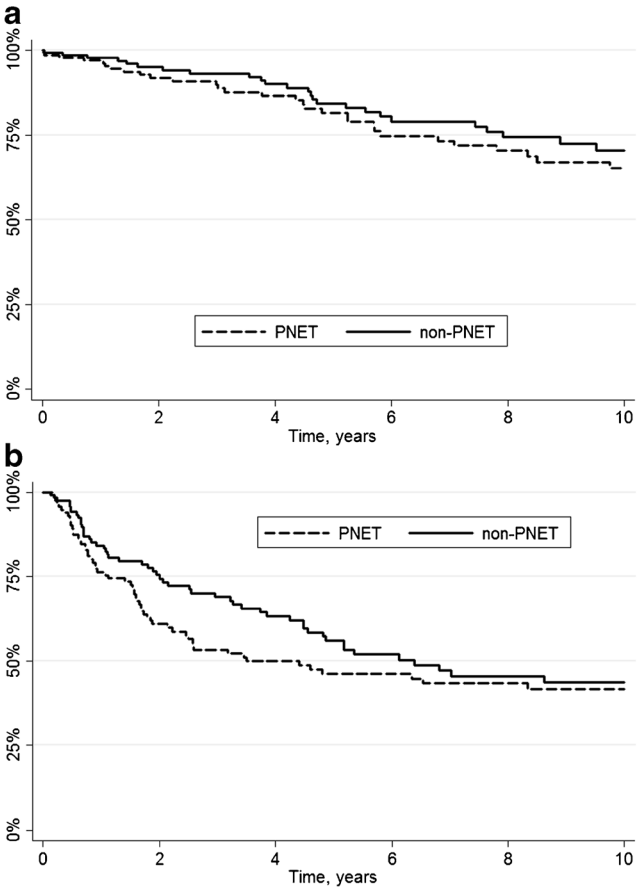

Fig. 2 **a** Kaplan-Meier survival OS curve comparing PNET vs. non-PNET-derived NELM NET after propensity score matching. **b** Kaplan-Meier survival DFS curve comparing PNET vs. non-PNET-derived NELM NET after propensity score matching

Propensity Score-Matched Analysis of Patients with NELM from PNET and Non-PNET

A propensity score matching analysis was then performed to minimize confounding and create more comparable cohorts of

Table 2 Univariate 10-year overall survival analysis of the study cohort ($n = 421$)

Variable	OS at 10 years (%)	95% CI	p value
Whole cohort	65.2	58.5–70.9	–
Age			0.12
<65 years	80.9	71.6–87.5	
≥65 years	65.5	50.9–76.7	
Gender			0.33
Male	60.7	51.2–68.9	
Female	70.2	60.6–77.8	
Location of primary NET			0.008
Pancreas	58.2	48.2–66.9	
Other	71.6	62.6–78.8	
Functional status			<0.001
Non-functional	54.8	43.7–64.5	
Functional	75.0	63.3–83.4	
Grade of differentiation			0.001
Well	80.4	71.1–87.1	
Moderate	58.2	40.5–72.3	
Poor	51.9	33.2–67.8	
Primary tumor lymph node status			<0.001
N0	78.1	69.2–84.7	
N1	54.4	43.2–64.2	
Synchronous disease			0.07
No	70.7	60.4–78.7	
Yes	62.5	53.4–70.3	
Extrahepatic disease			<0.001
No	67.8	60.8–73.8	
Yes	42.8	23.2–61.2	
Treatment before liver surgery			<0.001
None	64.8	56.5–71.9	
Octreotide	91.0	76.9–96.7	
Chemotherapy	39.4	12.9–65.3	
Intraoperative tumor ablation			0.31
No	67.1	59.7–73.4	
Yes	58.5	41.4–72.1	
Liver involvement			0.027
>75%	58.4	46.5–68.6	
75–50%	66.6	53.8–76.6	
50–25%	71.0	56.4–81.5	
<25%	92.3	56.6–98.9	
Location of liver metastasis			0.17
Unilobar	54.8	41.9–66.0	
Bilobar	62.4	52.6–70.8	
Margin status			<0.001
R0	71.7	63.8–78.2	
R1	56.7	41.3–69.5	
R2	28.0	6.9–54.6	
Adjuvant therapy			<0.001
None	71.0	61.1–78.9	
Octreotide	56.2	38.3–70.7	
Chemotherapy	33.5	15.1–53.3	

patients in the PNET and non-PNET groups (Table 3). After propensity matching for gender, grade of tumor differentiation, lymph node status, functional status, synchronous disease, preoperative treatment, liver involvement, extrahepatic disease, margin status, and adjuvant treatment, the propensity-matched cohort included 264 patients. After propensity matching, demographic and clinicopathologic characteristics of the two groups were comparable, including lymph nodes status ($p = 0.66$), presence of extrahepatic disease ($p = 0.48$), and tumor differentiation ($p = 0.09$). With a median follow-up of 5.1 years, the 5-year DFS and OS of patients with PNET-derived NELM and non-PNET derived NELM were comparable (DFS, PNET 46.2% vs. non-PNET 55.9%; $p = 0.22$ and OS, PNET 81.5% vs. non-PNET 84.3%; $p = 0.19$) (Fig. 2). In the multivariable Cox model, while the presence of extrahepatic disease and tumor grade were associated with DFS (extrahepatic disease, HR 2.12, 95% CI, 1.19–3.75, $p = 0.010$; tumor grade, HR 1.91, 95% CI, 1.43–2.55, $p < 0.001$) and OS (extrahepatic disease, HR 3.09, 95% CI, 1.65–5.79, $p < 0.001$; tumor grade, HR 1.76, 95% CI, 1.25–2.48, $p = 0.001$), primary tumor location was not associated with long-term outcome (DFS, HR 0.92, 95% CI, 0.60–1.42; OS, HR 0.93, 95% CI, 0.58–1.49; both $p > 0.05$).

Discussion

Previously regarded as rare, the incidence of GEP-NET is increasing worldwide ranging from 2.5 to 4.5 per 100,000.[9] The most common gastro-entero-pancreatic neuroendocrine tumors are carcinoid, insulinomas, gastrinomas, somatostatinomas, glucagonomas, and vipomas. NET can be either sporadic or part of the multiple neuroendocrine neoplasia type 1 (MEN type 1) syndrome. While many NET are indolent, up to 60–90% of patients develop liver metastasis during the course of their disease.[2] Given the importance of NELM in the natural history of NET, we sought to evaluate the outcome of patients with NELM arising from different primary NET sites, undergoing curative intent liver surgery, with a particular emphasis on examining the impact of PNET vs. non-PNET derived primary tumors. In particular, the current study was important because we demonstrated that many of the clinicopathological characteristics of patients with PNET vs. non-PNET-derived NELM were different. In turn, while the PNET primary tumor site appeared to be associated with a worse long-term outcome, on propensity score analysis primary tumor site was no longer associated with either DFS or OS.

On univariable analysis, patients with PNET-derived NELM had a worse 5-year DFS and OS compared with patients who had non-PNET-derived NELM (DFS, PNET 36.2% vs. non-PNET 55.2%; $p = 0.001$ and OS, PNET 79.5% vs. non-PNET 83.4%; $p = 0.008$). Importantly, several baseline clinicopathological characteristics of patients with PNET vs. non-PNET-derived NELM were different. In particular, patients with PNET-derived NELM were more likely to have non-functional, moderate-to-poorly differentiated tumors. In contrast, patients with non-PNET-derived NELM more often had extrahepatic disease and other characteristics typically considered less prognostically favorable.[23] However, similar to colorectal liver metastasis, the presence of extrahepatic disease should not be considered a strict contraindication to surgical resection of NELM. In fact, while the

Table 3 Clinical and pathologic features of patients after propensity score matching ($n = 264$)

Variables	Pancreas *N* (%)	Non-pancreas *N* (%)	*p* value
Patients	132	132	–
Age, median (IQR)	60.8 years (50.1–71.5)	61.8 years (53.0–67.0)	0.54
Gender			0.71
Female	72 (48.9)	75 (51.0)	
Male	60 (51.3)	57 (48.7)	
Functional status			0.70
Non-functional	59 (52.7)	53 (47.3)	
Functional	46 (50.0)	46 (50.0)	
NA/missing	27	33	
Grade of differentiation			0.09
Well	80 (51.3)	76 (48.7)	
Moderate	33 (57.9)	24 (42.1)	
Poor	19 (37.3)	32 (62.7)	
Primary tumor lymph node status			0.66
N0	54 (49.5)	55 (50.5)	
N1	64 (52.5)	58 (47.5)	
Synchronous disease			0.31
No	45 (45.9)	53 (54.1)	
Yes	87 (52.4)	79 (47.6)	
Treatment before liver surgery			0.85
None	85 (49.7)	86 (50.3)	
Octreotide	23 (47.9)	25 (52.1)	
Chemotherapy	8 (61.5)	5 (38.5)	
NA	16	16	
Liver involvement			0.84
>75%	5 (50.0)	5 (50.0)	
75–50%	27 (52.9)	24 (47.1)	
50–25%	35 (44.9)	43 (55.1)	
>25%	50 (47.6)	55 (52.4)	
NA/missing	15	5	
Location			0.62
Unilobar	62 (51.7)	58 (48.3)	
Bilobar	70 (48.6)	74 (51.4)	
Intraoperative tumor ablation			0.66
No	105 (49.5)	107 (50.5)	
Yes	26 (53.1)	23 (46.9)	
NA/missing	1	2	
Extrahepatic disease			0.48
No	124 (50.6)	121 (49.4)	
Yes	8 (42.1)	11 (57.9)	
Margin status			0.83
R0	89 (48.9)	93 (51.1)	
R1	25 (47.2)	28 (52.8)	
R2	10 (55.6)	8 (44.4)	
NA/missing	8	3	
Adjuvant therapy			0.07
None	77 (50.0)	77 (50.0)	
Octreotide	38 (44.7)	48 (55.3)	
Chemotherapy	17 (70.8)	7 (29.2)	
Disease-free survival, 5 years (95% CI)	46.2% (36.0–55.7)	55.9% (45.4–65.3)	0.22
Overall survival, 5 years (95% CI)	81.5% (72.3–87.9)	84.3% (75.5–90.1)	0.19

NA/missing not available/missing

presence of extrahepatic disease was associated with poor prognosis, curative intent resection in the presence of extraheptic disease should be considered when the disease is limited and an R0 resection is possible. The non-functional nature of PNET-derived NELM was another factor that has been associated with a worse prognosis.[17] Specifically, Spolverato et al. reported a Markov decision model to estimate and compare the cost-effectiveness associated with different management strategies (i.e., hepatic resection vs. intra-arterial therapy) for a simulated cohort of patients with NELM.[17] In that study, using a lifetime horizon analysis, patients with asymptomatic NELM had a worse overall survival after hepatic resection.[17]

Other reported clinicopathological prognostic factors of NELM that have been associated with a poor prognosis include R1 resection margin,[24] large hepatic tumor size,[24]

positive margin status,[10] poor tumor differentiation,[24] synchronous disease,[19] and extrahepatic disease.[19] The effect of primary tumor site has been more controversial. Most studies have examined cohorts that were predominantly derived from patients with either PNET or non-PNET gastrointestinal NET tumors.[10–27] As such, the impact of primary tumor site has not been specifically investigated as a prognostic factor in many previous studies. In those studies that have examined primary tumor site as an independent variable, some reports have noted that tumor site was indeed an important long-term prognostic factor.[18] In fact, in the current study, we similarly noted that patients with PNET-derived NELM had a markedly worse 10-year OS of 58.2% (95% CI, 48.2–66.9) vs. 71.6% (95% CI, 62.6–78.8) for patients with non-PNET-derived NELM ($p = 0.008$). However, given the varied baseline characteristics of patient with PNET vs. non-PNET tumors, direct comparisons of these cohorts may be problematic. As such, propensity score matching was utilized to help eliminate the residual confounding effect of other potential clinicopathological variables that might have impacted prognosis. Importantly, after propensity matching, both 5-year DFS and OS were comparable among patients with PNET and non-PNET derived NELM (DFS, PNET 46.2% vs. non-PNET 55.9%; $p = 0.22$ and OS, PNET 81.5% vs. non-PNET 84.3%; $p = 0.19$). Moreover, in the multivariable Cox model, while the presence of extrahepatic disease and tumor grade were associated with DFS and OS, primary tumor location was not associated with long-term outcomes. As such, the data strongly suggest that any potential effect of primary tumor site on prognosis was likely due to differences in underlying tumor biology and not the origin site of the tumor itself.

Our findings further define the characteristics of NELM and the impact of the varied tumor features on prognosis after liver resection. Patients with PNET-derived NELM were more likely to have non-functional disease compared with patients who had non-PNET-derived NELM, highlighting the importance of close follow-up to early detect liver metastases. Indeed, as noted in the current study, patients with non-functional liver metastases may have a worse long-term outcome.[17] In addition, while a simple comparison of PNET vs. non-PNET NELM patients suggested a worse long-term outcome for PNET patients, on matched analysis, primary tumor site did not impact prognosis. As such, primary tumor location should not necessarily inform decisions around prognosis and do not have an influence on survival such as other factors including the presence of extrahepatic disease or tumor grade.

This study has several limitations that should be considered when interpreting the results. The study design likely resulted in some selection bias, as with all retrospective reports. In addition, the multi-institutional nature of the cohort that included different centers in Europe and the USA increased the heterogeneity of patient selection criteria and treatment for NELM. However, the use of a large, multicenter data set increased the sample size and also improved the generalizability of the findings. Among patients with functional PNET, data on the type of tumor (i.e., gastrinoma, insulinoma, etc.) and hormonal levels were also not available. Moreover, in the present study, only patients who underwent curative intent liver surgery for NELM were included; patients who underwent palliative surgery, systemic or non-operative locoregional therapy were not assessed. As such, the findings of the current study may not pertain to these other clinical settings.

In conclusion, patients with PNET had a worse prognosis compared with patients who had non-PNET NELM on univariable analysis. Patients with PNET- vs. non-PNET-derived NELM had, however, different clinicopathological characteristics associated with their tumors. In particular, patients with PNET tumors were more likely to present with non-functional NELM and worse tumor grade. After accounting for potential confounding biases on propensity-matched analysis, primary tumor location was not associated with prognosis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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